Proteomics in the ALS–FTD Spectrum Disorders

Subjects: Neurosciences

Contributor: Francesca Vignaroli, Angelica Mele, Giacomo Tondo, Veronica De Giorgis, Marcello Manfredi, Cristoforo Comi, Letizia Mazzini, Fabiola De Marchi

Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are severely debilitating and progressive neurodegenerative disorders. A distinctive pathological feature of several neurodegenerative diseases, including ALS and FTD, is the deposition of aberrant protein inclusions in neuronal cells, which leads to cellular dysfunction and neuronal damage and loss Protein aggregate analysis, the identification of aggregated abnormal protein interactions and of proteins with an anomalous quaternary structure, may help to identify the pathological mechanisms involved in ALS–FTD. Several proteomic-based studies have been carried out on ALS–FTD spectrum disorders to explore the relevance of disease-related proteins and their potential roles in clinical practice. In ALS, aberrant protein folding and the formation of toxic protein aggregates are two crucial biological features. Indeed, the incorrect assembly of the protein in its native form leads to toxic molecules that potentially cause an overload of the degradation machine.

Keywords: neurodegenerative diseases ; amyotrophic lateral sclerosis ; frontotemporal dementia

1. Proteomics in Cellular and Animal Models

The recent acceleration in the discovery of new genes related to ALS–FTD spectrum disorders led to the need to develop strategies to identify the molecular pathways and proteostasis dysfunctions related to them, taking advantage of cellular and animal models [1]. Regarding cellular models, different studies included mutant C9orf72, SOD1, and TDP-43 and aimed to reproduce some conditions which characterize ALS and FTD, such as protein aggregation, mitochondrial dysfunction, and cellular toxicity.

Hartmann et al. [2] explored the neural interactions between the cytoplasmatic and nucleolar compartments in patients with C9orf72 mutations. They found that the overexpression of nucleolar aggregates associated with the C9Orf72 mutations reduced the number of synaptic proteins detected with proteomics. Other mechanisms associated with C9orf72 pathologies were discovered, such as the defects in stress granule homeostasis [3]. Boeynaems et al. [3] identified an active role for arginine-rich domains in this process, as they are able to induce a change in RNA and granule metabolism as well as spontaneous stress granule assembly. In addition, proteomics analysis of fibroblasts in ALS patients carrying the C9orf72 mutation revealed alterations in glucose metabolism and protein homeostasis. In fact, many proteins involved in the translation mechanism were powerfully downregulated in these cells compared with fibroblasts from wild-type ALS patients [4]. Motoneurons from C9orf72 patient-derived iPSCs have also altered mitochondrial axonal transport, impaired mitochondrial metabolism, and shorter axons [5].

Similarly, other cellular studies identified SOD1 and TDP-43 [6][7] protein interactions. McAlary, using a cell-based assays approach, showed that the aggregation of SOD1 variants is well-correlated to cellular toxicity even without a subsequent correlation with disease severity. Instead, in regard to TDP-43, the group of Rogelj [7] indicated that TDP-43 is an important regulator of RNA metabolism and intracellular transport in ALS–FTD, observing that proteins related to cellular processes (Ran-binding protein 1, DNA methyltransferase 3 alpha and chromogranin B) were downregulated upon TDP-43 knockdown.

Animal models can also validate these genetic and biological alterations [1]. In astrocytes from the ALS mouse model overexpressing human SOD1(G93A), a correlation between proteome and secreted metabolome involved in glutathione metabolism was observed. This finding has been speculated to be responsible for altered astrocyte functions due to a depletion of proteins and secreted metabolites [8].

In addition, in SOD1(G93A) in murine spinal cords, the interactor of misfolded SOD1 (e.g., HSPA8 and Na+/K+ATPAse-alfa3) had impaired activity that contributed to motor neuron vulnerability [9]. Furthermore, considering the mutated zebrafish, mutations in cyclin F were observed, which also provided high levels of activated caspase-3 and other proteins

negatively involved with cellular survival [10]. However, due to the absence of precise animal models carrying the other mutations mentioned, there are no significant proteomics studies in other animal models.

2. Proteomics in Human Samples

2.1. Cerebrospinal Fluid

CSF represents a potential source of biomarkers because it is in contact with the brain's interstitial fluid. In addition, changes in the CSF protein content can reflect alterations in proteins' expressions within the central nervous system [11]. Various studies explored CSF's potential diagnostic biomarkers for the ALS–FTD spectrum using proteomic analysis and by comparing data in patients and controls to characterize the proteomic profile of ALS–FTD samples.

The pioneering study of Ranganathan and colleagues [12] compared the proteomic CSF profile of ALS patients and controls using surface-enhanced laser desorption ionization-time of flight mass spectrometry. Three major CSF biomarkers were identified that were significantly different between patients and controls: the carboxy-terminal fragment of neuroendocrine protein 7B2, which was increased in patients and is involved in the maturation and release of hormones, neuropeptides, and growth factors; transthyretin and cystatin C, which were decreased in patients and are involved in neuroprotection and extracellular proteins homeostasis. Several subsequent studies analyzing the CSF proteome profile with different techniques revealed panels of candidate biomarkers in ALS, including zinc- and iron-binding proteins involved in many metabolic processes [13][14] as well as proteins associated with synaptic regulation, apoptosis, extracellular matrix regulation, and neuroinflammation [15][16][17].

The analysis of proteome profiles has been tested in the diagnostic workup of ALS compared with controls and patients affected by other neurological diseases [18][19][20][21][22], showing differentiation between the profiles of ALS patients and non-ALS conditions with good sensitivity and excellent specificity [18][23].

An early study in FTD patients compared with controls identified significant differences in several CSF proteins, including the Zn-alpha-2-glycoprotein, whose levels were increased in patients [24]. Intriguingly, the same findings were reported a few years later in ALS patients in the study of Brettschneider and colleagues, again suggesting possible common pathogenic protein profiles along the ALS–FTD spectrum [14]. In FTD, the proteomic approach has been shown to potentially aid the differential diagnosis. A comparative proteomic analysis documented differences in the expression of CSF protein profiles in FTD patients compared to controls and Alzheimer's disease patients, thus suggesting a different pathophysiological background between the two dementia disorders [25]. As for ALS, profiling CSF proteins in genetic FTD cases may aid in tracking pathophysiological changes during different disease phases. A proteomic approach using mass spectrometry was used in presymptomatic and symptomatic carriers of the granulin (GRN) mutation and healthy noncarriers. Differences in CSF protein expression were not only revealed between symptomatic GNR-mutated and noncarriers, but also between presymptomatic and symptomatic GNR-mutated carriers, including proteins involved in synaptic activity, vesicle secretion, and inflammatory responses [26].

A key point for proteomic studies is the possibility of detecting biomarkers for disease progression and prognostic value. A longitudinal study analyzing the CSF of 14 ALS patients using data-independent acquisition mass spectrometry and evaluating data through mathematical modeling identified changes in 28 peptides involved in stress response and innate immunity as fixed effects in disease progression [27]. Several proteins' CSF changes have been associated with disease severity, disease progression, and survival [11][12][21]), but the importance of their prognostic role still requires further confirmation. The studies on cerebrospinal fluid are summarized in **Table 1**.

2.2. Blood

Few studies applied proteomic analysis to identify changes in serum proteins in the ALS–FTD spectrum and mainly focused on exploring neuroinflammatory responses and their corresponding peripheral mechanisms. Neuroinflammation is widely recognized as a common mechanism in neurodegenerative conditions, representing a promising target for modulatory therapies aiming to stop or slow neuronal loss [28]. Cao and colleagues [29] compared more than one hundred markers of inflammation, including cytokines, growth factors, and blood–brain barrier breakdown markers in the serums of ALS patients to controls. The authors identified the 20 most changed proteins, which were mainly represented by proangiogenic and growth factors, thus suggesting that altered glial activation and blood–brain barrier leakage may be involved in ALS pathogenesis. The detection of differences in the serum levels of acute phase reactants in ALS patients than in controls has been reported by another study [30], together with changes in lipid homeostasis proteins, thus supporting the hypothesis of a metabolic shift towards increased peripheral use of lipids in ALS patients and suggesting the involvement of lipid homeostasis in the disease [30]. Serum protein changes were also correlated with specific

characteristics of the disease. ALS patients with cognitive impairment showed a different serum proteomic profile than ALS patients without cognitive impairment, especially involving proteins within the coagulation and immune pathways, confirming the utility of proteomic analysis as a tool to study disease-specific features [31]. Lastly, protein changes in the serum of both FTD and ALS patients compared to controls were analyzed in the study of Katzeff and colleagues [32]. The authors found 23 serum proteins, mainly involved in innate immunity and calcium signaling, dysregulated in bvFTD patients and 14 in ALS patients as compared to controls. Intriguingly, 11 of these proteins were altered in both diseases, suggesting possible common pathophysiology pathways between ALS and FTD [32]. The studies on blood are summarized in **Table 1**.

Table 1. Cerebrospinal fluid and blood studies on ALS–FTD spectrum disorders: methodology and main findings.

Disease	Year	Method	Main Findings
Cerebrospinal Fluid			
ALS vs. HC	**2005**	**surface-enhanced laser desorption ionization time-of-flight mass spectrometry**	- protein 7B2 increased in patients - transthyretin and cystatin C decreased in patients [12]
ALS vs. HC	**2012**	**two-dimensional difference in gel electrophoresis with matrix-assisted laser desorption ionization time-of-flight mass spectrometry**	- parkin-like and iron and zinc binding proteins increased in patients [13]
ALS (fast vs. slow)	**2010**	**two-dimensional difference in gel electrophoresis with matrix-assisted laser desorption ionization time-of-flight mass spectrometry**	- heat shock protein 1, alpha-1 antitrypsin, fetuin-A precursor, transferrin, transthyretin, and nebulin-related anchoring protein were higher in fast progressors [14]
ALS vs. HC	**2022**	**ultra-sensitive proximity extension assay**	- junctional adhesion molecule A protein, tumor necrosis factor receptor 2, and chitinase 1 were upregulated in patients - myoglobin was downregulated in patients [15]
ALS vs. HC	**2013**	**liquid chromatography-tandem mass spectrometry**	- elevated levels of chitotriosidase in patients [16]
ALS vs. HC	**2012**	**paramagnetic bead chromatography with matrix-assisted laser desorption ionization time-of-flight mass spectrometry**	- upregulation of secreted phosphoprotein 1 in patients [17]
ALS vs. HC and other neurodegenerative diseases	**2015**	**label-free liquid chromatography-tandem mass spectrometry**	- pathways altered for protein 63, amyloid-like protein 1, SPARC-like protein 1, and cell adhesion molecule 3 in ALS patients [18]
ALS vs. other neurological diseases	**2020**	**liquid chromatography-tandem mass spectrometry**	- CXC motif chemokine ligand 12 increased in patients [19]
ALS vs. HC and Parkinson's disease	**2019**	**targeted multiple reaction monitoring (MRM) mass spectrometry**	- levels of ubiquitin carboxy-terminal hydrolases, such as protein 1, glycoprotein non-metastatic melanoma protein B, and cathepsin D were increased in patients [20]

Disease	Year	Method	Main Findings
Cerebrospinal Fluid			
ALS vs. HC and other neurodegenerative diseases	**2016**	**two-dimensional liquid chromatography mass spectrometry**	- insulin-like growth factor II was significantly downregulated in ALS patients - glutamate receptor 4 was significantly upregulated in patients [21]
ALS vs. HC and neuropathies	**2008**	**two-dimensional gel electrophoresis**	- differential expression of ceruloplasmin isoforms in ALS patients compared to HC - increase in the relative abundance of more basic ceruloplasmin forms, corresponding to nonsialylated proteins in patients [22]
ALS vs. other neurological diseases	**2009**	**Bio-Plex human 27-plex panel of cytokines and growth factors with atomic absorption spectroscopy**	- a panel of interleukins (i.e., IL6, IL2, IL16, and IL17) were higher in ALS compared to others [23]
ALS	**2020**	**shotgun proteomics and data-independent acquisition mass spectrometry**	- in a longitudinal follow up, changes in abundance from 28 peptides [27]
FTD vs. HC	**2004**	**prefractionation method with two-dimensional electrophoresis**	- Zn-alpha-2-glycoprotein increased in patients [24]
FTD vs. HC and AD	**2002**	**Two-dimensional gel electrophoresis with mass spectrometry**	- granin-like neuroendocrine precursor, pigment-epithelium derived factor, retinol-binding protein, apoE, haptoglobin, and albumin levels altered in FTD patients [25]
FTD (GRN carriers vs. non-carriers)	**2019**	**parallel reaction monitoring mass spectrometry**	- symptomatic GRN mutation carriers had lower levels of neuronal pentraxin receptor, receptor-type tyrosine-protein phosphatase N2, neurosecretory protein VGF, chromogranin-A, and V-set and transmembrane domain-containing protein 2B than presymptomatic carriers and noncarriers [26]
		Blood	
ALS vs. HC	**2022**	**cytometric bead array and proteome profiling**	- fractalkine, BDNF, EGF, PDGF, Dkk-1, MIF and angiopoietin-2, S100β were unchanged in ALS serum [29]
ALS vs. HC	**2017**	**bi-dimensional electrophoresis and mass spectrometry**	- acute phase reactants and lipid homeostasis proteins were higher in ALS [30]
ALS vs. HC	**2018**	**nano-liquid chromatography and time-of-flight mass spectrometry**	- the LXR/RXR and coagulation pathways were downregulated in LAS - the complement pathway was upregulated - differences between ALS patients with and without cognitive impairment [31]

Disease	Year	Method	Main Findings
Cerebrospinal Fluid			
ALS vs. FTD vs. HC	**2020**	**nano-capillary liquid chromatography–tandem mass spectrometry**	- 23 proteins were altered in FTD vs. HC (increased: APOL1, C3, CTSH, EIF5A, MYH2, S100A8, SUSD5, WDR1; decreased: C1S, C7, CILP2, COMP, CRTAC1, EFEMP1, FBLN1, GSN, HSPG2, IGHV1, ITIH2, PROS1, SHBG, UMOD, VASN) - 14 proteins were altered in ALS vs. HC (increased: APOL1, CKM, CTSH, IGHG1, IGKC, MYH2; decreased: C7, COMP, CRTAC1, EFEMP1, FBLN1, GSN, HSPG2, SHBG) [32]

CSF: cerebrospinal fluid; ALS: amyotrophic lateral sclerosis; HC: healthy controls; FTD: frontotemporal dementia; AD: Alzheimer's disease; GRN: progranulin.

2.3. Other Tissues

ALS and FTD are pathologically characterized by the presence of protein inclusions due to dysregulation in protein expression, processing, or degradation. In light of this, the proteomic analysis of post-mortem samples, such as from the cortex and spinal cord, can help to delineate the molecular changes in protein composition in ALS–FTD patients.

In 2011, Gozal et al. conducted a proteomic analysis of hippocampal dentate granule cells in sporadic FTD subjects by using a combined approach consisting of laser capture microdissection and high-resolution liquid chromatography-tandem mass spectrometry. Compared to controls, they identified 1252 proteins in hippocampal dentate granule cells of FTD patients. Additionally, SEPT11, a protein associated with the cytoskeleton, was a component of protein inclusions with the well-known TDP-43 protein. These findings highlighted the cytoskeleton-associated protein's possible role in FTD pathogenesis [33][34]. Interestingly, the analysis also showed that proteins not associated with protein inclusions presented a dysregulated expression [33][34].

Instead, to better understand the pathogenic role of the reduction of C9orf72 expression in FTD patients, a proteomic approach was applied to determine the level of reduction in the long and short isoforms of C9orf72 in the frontal cortices of mutated patients. The results showed that the C9Orf72 long isoform was significantly decreased in the frontal cortices of genetic patients compared to normal subjects [35].

In ALS patients, spinal cord protein profiles revealed dysregulated expression in proteins involved in mitochondrial, calcium, and protein metabolism. In particular, ATP5D (a subunit of ATP synthase that is essential for ATP production) was reduced mainly at synapses, supporting the role of synaptic dysfunction in ALS pathogenesis. In addition, the level of calmodulin, a protein implicated in calcium metabolism, was downregulated, which determined the disruption of calcium homeostasis [36]. Moreover, protein acetylation seems to be differentially regulated: for example, the glial fibrillary acid protein (a GFAP-component of the filament of astrocytes that plays a role in astrocyte-neuron interaction) was found to be heavily acetylated and upregulated in an ALS patient's spinal cord, suggesting a potential neuroprotective effect of histone deacetylase inhibitors [37].

The proteomic analysis of post-mortem samples was also applied to investigate the molecular basis of the pathological overlap between ALS and FTD. With an elegant study published in 2018, Umoh et al. showed the comparison of protein expression in frontal cortical tissue from post-mortem ALS, FTD, and ALS–FTD cases, revealing different coexpressed proteins involved in synaptic transmission, inflammation, and RNA metabolism across the ALS–FTD spectrum. Furthermore, ALS cases carrying the C9orf72 mutation presented an increase in proteins associated with astrocytes and microglia compared to sporadic cases, implying that genetic expansion could also alter the inflammatory response [38]. In addition, Iridoy et al. in the same year compared protein composition in the spinal cords of ALS and FTD patients, showing that ALS and FTD partially shared molecular and functional alterations with a common impairment in mitochondrial metabolism. However, parts of the altered protein expression, such as galectin 2, transthyretin, and protein S100-A6 for ALS, remained disease-specific [39].

References

1. Cheng, F.; De Luca, A.; Hogan, A.L.; Rayner, S.L.; Davidson, J.M.; Watchon, M.; Stevens, C.H.; Muñoz, S.S.; Ooi, L.; Yerbury, J.J.; et al. Unbiased label-free quantitative proteomics of cells expressing amyotrophic lateral sclerosis (ALS) mutations in CCNF reveals activation of the apoptosis pathway: A workflow to screen pathogenic gene mutations. Front. Mol. Neurosci. 2021, 14, 627740.
2. Hartmann, H.; Hornburg, D.; Czuppa, M.; Bader, J.; Michaelsen, M.; Farny, D.; Arzberger, T.; Mann, M.; Meissner, F.; Edbauer, D. Proteomics and C9orf72 neuropathology identify ribosomes as poly-GR/PR interactors driving toxicity. Life Sci. Alliance 2018, 1, e201800070.
3. Boeynaems, S.; Bogaert, E.; Kovacs, D.; Konijnenberg, A.; Timmerman, E.; Volkov, A.; Guharoy, M.; De Decker, M.; Jaspers, T.; Ryan, V.H.; et al. Phase separation of C9orf72 dipeptide repeats perturbs stress granule dynamics. Mol. Cell 2017, 65, 1044–1055.
4. Lualdi, M.; Shafique, A.; Pedrini, E.; Pieroni, L.; Greco, V.; Castagnola, M.; Cucina, G.; Corrado, L.; Di Pierro, A.; De Marchi, F.; et al. C9ORF72 repeat expansion affects the proteome of primary skin fibroblasts in ALS. Int. J. Mol. Sci. 2021, 22, 10385.
5. Mehta, A.R.; Gregory, J.M.; Dando, O.; Carter, R.N.; Burr, K.; Nanda, J.; Story, D.; McDade, K.; Smith, C.; Morton, N.M.; et al. Mitochondrial bioenergetic deficits in C9orf72 amyotrophic lateral sclerosis motor neurons cause dysfunctional axonal homeostasis. Acta Neuropathol. 2021, 141, 257–279.
6. McAlary, L.; Aquilina, J.A.; Yerbury, J.J. Susceptibility of mutant SOD1 to form a destabilized monomer predicts cellular aggregation and toxicity but not in vitro aggregation propensity. Front. Neurosci. 2016, 10, 499.
7. Štalekar, M.; Yin, X.; Rebolj, K.; Darovic, S.; Troakes, C.; Mayr, M.; Shaw, C.E.; Rogelj, B. Proteomic analyses reveal that loss of TDP-43 affects RNA processing and intracellular transport. Neuroscience 2015, 293, 157–170.
8. Stella, R.; Bonadio, R.S.; Cagnin, S.; Massimino, M.L.; Bertoli, A.; Peggion, C. Perturbations of the Proteome and of Secreted Metabolites in Primary Astrocytes from the hSOD1 (G93A) ALS Mouse Model. Int. J. Mol. Sci. 2021, 22, 7028.
9. Ruegsegger, C.; Maharjan, N.; Goswami, A.; Filézac de L'Etang, A.; Weis, J.; Troost, D.; Heller, M.; Gut, H.; Saxena, S. Aberrant association of misfolded SOD1 with Na+/K+ ATPase-α3 impairs its activity and contributes to motor neuron vulnerability in ALS. Acta Neuropathol. 2016, 131, 427–451.
10. Hogan, A.L.; Don, E.K.; Rayner, S.L.; Lee, A.; Laird, A.S.; Watchon, M.; Winnick, C.; Tarr, I.S.; Morsch, M.; Fifita, J.A.; et al. Expression of ALS/FTD-linked mutant CCNF in zebrafish leads to increased cell death in the spinal cord and an aberrant motor phenotype. Hum. Mol. Genet. 2017, 26, 2616–2626.
11. Brettschneider, J.; Mogel, H.; Lehmensiek, V.; Ahlert, T.; Süssmuth, S.; Ludolph, A.C.; Tumani, H. Proteome analysis of cerebrospinal fluid in amyotrophic lateral sclerosis (ALS). Neurochem. Res. 2008, 33, 2358–2363.
12. Ranganathan, S.; Williams, E.; Ganchev, P.; Gopalakrishnan, V.; Lacomis, D.; Urbinelli, L.; Newhall, K.; Cudkowicz, M.E.; Brown, R.H., Jr.; Bowser, R. Proteomic profiling of cerebrospinal fluid identifies biomarkers for amyotrophic lateral sclerosis. J. Neurochem. 2005, 95, 1461–1471.
13. Mendonça, D.M.F.; Pizzati, L.; Mostacada, K.; de S. Martins, S.C.; Higashi, R.; Ayres Sá, L.; Moura Neto, V.; Chimelli, L.; Martinez, A.M. Neuroproteomics: An insight into ALS. Neurol. Res. 2012, 34, 937–943.
14. Brettschneider, J.; Lehmensiek, V.; Mogel, H.; Pfeifle, M.; Dorst, J.; Hendrich, C.; Ludolph, A.C.; Tumani, H. Proteome analysis reveals candidate markers of disease progression in amyotrophic lateral sclerosis (ALS). Neurosci. Lett. 2010, 468, 23–27.
15. Sjoqvist, S.; Otake, K. A pilot study using proximity extension assay of cerebrospinal fluid and its extracellular vesicles identifies novel amyotrophic lateral sclerosis biomarker candidates. Biochem. Biophys. Res. Commun. 2022, 613, 166–173.
16. Varghese, A.M.; Sharma, A.; Mishra, P.; Vijayalakshmi, K.; Harsha, H.C.; Sathyaprabha, T.N.; Bharath, S.M.; Nalini, A.; Alladi, P.A.; Raju, T.R. Chitotriosidase-a putative biomarker for sporadic amyotrophic lateral sclerosis. Clin. Proteom. 2013, 10, 19.
17. Von Neuhoff, N.; Oumeraci, T.; Wolf, T.; Kollewe, K.; Bewerunge, P.; Neumann, B.; Brors, B.; Bufler, J.; Wurster, U.; Schlegelberger, B.; et al. Monitoring CSF proteome alterations in amyotrophic lateral sclerosis: Obstacles and perspectives in translating a novel marker panel to the clinic. PLoS ONE 2012, 7, e44401.
18. Collins, M.A.; An, J.; Hood, B.L.; Conrads, T.P.; Bowser, R.P. Label-Free LC–MS/MS proteomic analysis of cerebrospinal fluid identifies Protein/Pathway alterations and candidate biomarkers for amyotrophic lateral sclerosis. J. Proteome Res. 2015, 14, 4486–4501.

19. Andrés-Benito, P.; Povedano, M.; Domínguez, R.; Marco, C.; Colomina, M.J.; López-Pérez, Ó.; Santana, I.; Baldeiras, I.; Martínez-Yelámos, S.; Zerr, I.; et al. Increased CXC motif chemokine ligand 12 levels in cerebrospinal fluid as a cand idate biomarker in sporadic amyotrophic lateral sclerosis. Int. J. Mol. Sci. 2020, 21, 8680.

20. Zhu, S.; Wuolikainen, A.; Wu, J.; Öhman, A.; Wingsle, G.; Moritz, T.; Andersen, P.M.; Forsgren, L.; Trupp, M. Targeted multiple reaction monitoring analysis of CSF identifies UCHL1 and GPNMB as candidate biomarkers for ALS. J. Mol. N eurosci. 2019, 69, 643–657.

21. Chen, Y.; Liu, X.; Wu, J.; Ren, H.; Wang, J.; Ding, Z.T.; Jiang, Y.P. Proteomic analysis of cerebrospinal fluid in amyotrop hic lateral sclerosis. Exp. Ther. Med. 2016, 11, 2095–2106.

22. Conti, A.; Iannaccone, S.; Sferrazza, B.; De Monte, L.; Cappa, S.; Franciotta, D.; Olivieri, S.; Alessio, M. Differential exp ression of ceruloplasmin isoforms in the cerebrospinal fluid of amyotrophic lateral sclerosis patients. PROTEOMICS–Cli n. Appl. 2008, 2, 1628–1637.

23. Mitchell, R.M.; Freeman, W.M.; Randazzo, W.T.; Stephens, H.E.; Beard, J.L.; Simmons, Z.; Connor, J.R. A CSF biomar ker panel for identification of patients with amyotrophic lateral sclerosis. Neurology 2009, 72, 14–19.

24. Hansson, S.F.; Puchades, M.; Blennow, K.; Sjögren, M.; Davidsson, P. Validation of a prefractionation method followed by two-dimensional electrophoresis–Applied to cerebrospinal fluid proteins from frontotemporal dementia patients. Prot eome Sci. 2004, 2, 7.

25. Davidsson, P.; Sjögren, M.; Andreasen, N.; Lindbjer, M.; Nilsson, C.L.; Westman-Brinkmalm, A.; Blennow, K. Studies of the pathophysiological mechanisms in frontotemporal dementia by proteome analysis of CSF proteins. Mol. Brain Res. 2002, 109, 128–133.

26. Van der Ende, E.L.; Meeter, L.H.; Stingl, C.; van Rooij, J.G.J.; Stoop, M.P.; Nijholt, D.A.T.; Sanchez-Valle, R.; Graff, C.; Öijerstedt, L.; Grossman, M.; et al. Novel CSF biomarkers in genetic frontotemporal dementia identified by proteomics. Ann. Clin. Transl. Neurol. 2019, 6, 698–707.

27. Mellinger, A.L.; Griffith, E.H.; Bereman, M.S. Peptide variability and signatures associated with disease progression in CSF collected longitudinally from ALS patients. Anal. Bioanal. Chem. 2020, 412, 5465–5475.

28. Comi, C.; Tondo, G. Insights into the protective role of immunity in neurodegenerative disease. Neural Regen. Res. 201 7, 12, 64.

29. Cao, M.C.; Cawston, E.E.; Chen, G.; Brooks, C.; Douwes, J.; McLean, D.; Graham, E.S.; Dragunow, M.; Scotter, E.L. S erum biomarkers of neuroinflammation and blood-brain barrier leakage in amyotrophic lateral sclerosis. BMC Neurol. 2 022, 22, 216.

30. De Benedetti, S.; Gianazza, E.; Banfi, C.; Marocchi, A.; Lunetta, C.; Penco, S.; Bonomi, F.; Iametti, S. Serum proteome in a sporadic amyotrophic lateral sclerosis geographical cluster. PROTEOMICS–Clin. Appl. 2017, 11, 1700043.

31. Xu, Z.; Lee, A.; Nouwens, A.; Henderson, R.D.; McCombe, P.A. Mass spectrometry analysis of plasma from amyotrophi c lateral sclerosis and control subjects. Amyotroph. Lateral Scler. Front. Degener. 2018, 19, 362–376.

32. Katzeff, J.S.; Bright, F.; Lo, K.; Kril, J.J.; Connolly, A.; Crossett, B.; Ittner, L.M.; Kassiou, M.; Loy, C.T.; Hodges, J.R.; et al. Altered serum protein levels in frontotemporal dementia and amyotrophic lateral sclerosis indicate calcium and immu nity dysregulation. Sci. Rep. 2020, 10, 13741.

33. Gozal, Y.M.; Dammer, E.B.; Duong, D.M.; Cheng, D.; Gearing, M.; Rees, H.D.; Peng, J.; Lah, J.J.; Levey, A.I. Proteomi c analysis of hippocampal dentate granule cells in frontotemporal lobar degeneration: Application of laser capture techn ology. Front. Neurol. 2011, 2, 24.

34. Gozal, Y.M.; Seyfried, N.T.; Gearing, M.; Glass, J.D.; Heilman, C.J.; Wuu, J.; Duong, D.M.; Cheng, D.; Xia, Q.; Rees, H. D.; et al. Aberrant septin 11 is associated with sporadic frontotemporal lobar degeneration. Mol. Neurodegener. 2011, 6, 1–13.

35. Viodé, A.; Fournier, C.; Camuzat, A.; Fenaille, F.; Bank, N.B.; Latouche, M.; Elahi, F.; Le Ber, I.; Junot, C.; Lamari, F.; et al. New antibody-free mass spectrometry-based quantification reveals that C9ORF72 long protein isoform is reduced in the frontal cortex of hexanucleotide-repeat expansion carriers. Front. Neurosci. 2018, 12, 589.

36. Engelen-Lee, J.; Blokhuis, A.M.; Spliet, W.G.M.; Pasterkamp, R.J.; Aronica, E.; Demmers, J.A.A.; Broekhuizen, R.; Nar do, G.; Bovenschen, N.; Van Den Berg, L.H.; et al. Proteomic profiling of the spinal cord in ALS: Decreased ATP5D leve ls suggest synaptic dysfunction in ALS pathogenesis. Amyotroph. Lateral Scler. Front. Degener. 2017, 18, 210–220.

37. Liu, D.; Liu, C.; Li, J.; Azadzoi, K.; Yang, Y.; Fei, Z.; Dou, K.; Kowall, N.W.; Choi, H.P.; Vieira, F.; et al. Proteomic analysi s reveals differentially regulated protein acetylation in human amyotrophic lateral sclerosis spinal cord. PLoS ONE 201 3, 8, e80779.

38. Umoh, M.E.; Dammer, E.B.; Dai, J.; Duong, D.M.; Lah, J.J.; Levey, A.I.; Glass, J.D.; Seyfried, N.T. A proteomic network approach across the ALS-FTD disease spectrum resolves clinical phenotypes and genetic vulnerability in human brain.

EMBO Mol. Med. 2018, 10, 48–62.

39. Iridoy, M.O.; Zubiri, I.; Zelaya, M.V.; Martinez, L.; Ausín, K.; Lachen-Montes, M.; Santamaría, E.; Fernandez-Irigoyen, J.; Jericó, I. Neuroanatomical quantitative proteomics reveals common pathogenic biological routes between amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Int. J. Mol. Sci. 2018, 20, 4.

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